del

(9

CELLULAR DIGESTION;

ITS UTILITY IN PATHOLOGICAL PROCESSES.

BY

N. S. DAVIS, Jr., A.M., M.D.,

OF CHICAGO, ILL.

[Reprinted from the "Transactions of the Ninth International Medical Congress," Vol. III.]

PRESS OF WM. F. FELL & CO., 1220-24 SANSOM ST., PHILA., PA.

Dr. N. S. Davis, Jr., of Chicago, Ill., presented a paper entitled :—

CELLULAR DIGESTION; ITS UTILITY IN PATHOLOGICAL PROCESSES.

DIGESTION CELLULAIRE; SON UTILITÉ DANS LES PROCÉDÉS PATHOLOGIQUES.

ZELLENVERDAUUNG; IHR NUTZEN IN PATHOLOGISCHEN PROZESSEN.

I offer the present paper, not because the views expressed therein are definitely proven, but hoping that they may be suggestive, and by discussion lead to an elucidation of some points now obscure.

In pathological processes cellular digestion is useful in the removal of foreign bodies, if we understand by foreign bodies such as are unnatural or no longer useful in the tissues. It is not every foreign body that is digestible; it is only those of organic origin. They consist chiefly of dead tissue, fibrin, ligatures, silk, cotton, etc. These substances, as it were, melt away under the influence of the living tissue about them. They are not soluble in the lymph or blood, as is readily shown by noticing that no change occurs on placing them in these fluids which have been drawn from the body, and are maintained at the bodily temperature.

Other insoluble substances exist that, when *imbedded* in living tissues, are slowly transported piecemeal and deposited elsewhere in the body, and often scattered widely in it. Such are pigments, charcoal, carmine, and silicious and calcareous substances. That this transportation is accomplished by the white blood cells, is a fact well established. The process is too well known to require illustration. This group of substances differs completely from the first one mentioned, in not undergoing true absorption, since the particles composing them remain in the tissues, though not perhaps where originally deposited. Substances of the first group disappear entirely.

The query naturally arises how are these insoluble substances so completely removed. That the vitality of the surrounding tissue is an all important element is evident, since, when the same substances are placed in dead tissue, no disappearance takes place. The authors of most text-books content themselves by simply saying that these bodies are capable of solution in the living body, without telling us how.

Within the last three or four years, almost simultaneously, several have tried to explain this disappearance of non-soluble bodies, upon the ground that they were digested by the living tissues, and chiefly, if not wholly, by the leucocytes, which mass themselves about foreign bodies and sources of irritation.

In 1884 I began to advocate this view to my students, for it seemed the most probable explanation of the phenomena. It was self evident that the presence of living tissue was essential, and the uniform presence of leucocytes covering and permeating the disappearing body suggested that their vital activity was the essential factor, and

that probably they acted as an organized ferment or digester. The existence of a non-organized ferment has been suggested but never proven.

A few months later the articles by Metchnikoff, which are now well known and which first appeared in "Rouskaia Medicina,"* on intra-cellular digestion, attracted my attention. To him belongs the credit of placing in form the theory of intra-cellular digestion as applied to insoluble but removable bodies. He did more than affirm this theory, for he cited proofs of such action by leucocytes and their analogues in invertebrates. All cells possessing this power he termed phagocytes. He found this function most fully developed in mesodermic cells, many of which are amœboid and devour foreign substances, for instance, elements already used and dead in the organism. The ability of leucocytes to take up and transport particles of foreign bodies has long been known, but Metchnikoff was the first to demonstrate their power of digesting some particles within themselves. This he showed in the atrophying tails of tadpoles,† which are filled with amœboid cells containing distinguishable particles of nerve and muscle fibres of varying size, according to the degree of intra-cellular digestion that has taken place. A similar removal of useless parts was observed in invertebrates.‡ In the lowest forms, the sponges and cœlenterates, the property of intra-cellular digestion is possessed by both ecto- and endo-dermic elements, and in those a little higher by mesodermic elements also. When the body to be removed was too large for a single cell to manage, several united, and thus produced what is analogous to the giant cells of vertebrates. Invertebrate cells were found to exercise a power of choice in regard to what they would thus appropriate.

These views have been placed before English readers most clearly and attractively by John Bland Sutton, in lectures§ delivered at the Royal College of Surgeons, London, in 1886, and since elaborated in the volume known as "An Introductory to General Pathology." ‖ Sutton cites additional illustrations of the power of intra-cellular digestion by the cells of invertebrates, and confirms the observations of Metchnikoff on the atrophying tails of tadpoles.

These observations enlarge the function of the leucocyte and make its analogy to the amœba perfect. For within the living body they lead an independent existence, taking up nourishment, doubtless, usually, in liquid form, but at times in the form of solids, which must be digested by them. They take within themselves these solids by movements of their protoplasm precisely similar to those of the amœba.

To illustrate intra-cellular digestion in pathological processes, mention may first be made of its utility in the removal of blood that has extravasated into the tissues. In such cases the liquid portion of the blood is rapidly removed through the lymph channels. A part of the solid cellular constituents is also thus removed. Another portion breaks down into a granular mass which causes the pigment of the red cells either to go into solution in the plasma, thereby producing characteristic staining of the surrounding tissues, or to crystallize and be deposited in them. The largest part, however, of the solid and cellular elements, as well as of the granular matter thus formed, is taken up by the leucocytes which rapidly fill the extravasated tissues. Not unfrequently, a perfect red corpuscle can be found within a leucocyte, and others in all stages of disintegration and dissolution can be seen there. The red corpuscles when thus swallowed diminish in size and gradually disappear, numerous minute granules of brown pigment being all that is left of them. Thus the leucocyte is transformed into

---

* Nos. 1, 3, 4, 5, 6, 1884.

† "Rouskaia Medicin a" No. 1, 1884, and *Revue des Sciences Médicales*, Tome xxv, p. 69.

‡ "Rouskaia Medicina," Nos. 3, 4, 5 and 6, 1884, and *Revue des Sciences Médicales*, Tome xxv, p. 70.

§ See *British Medical Journal*, 1886.

‖ Published in America by P. Blakiston, Son & Co., Philadelphia, 1886.

a pigment carrier which may transport the pigment granules to a considerable distance and cause finally their elimination from the system, or their deposition elsewhere. In the course of these changes, undoubtedly the dissolution of the stroma of the red cell is brought about by the power of the leucocyte of intra-cellular digestion.

We, without doubt, see this same power exerted in the removal of fibrinous clots and exudates. For example, the fibrin which forms a thrombus may be thus removed, although it is liable to other methods of disposal. It may shrink into a dense compact mass, and thus remain almost indefinitely or undergo calcification. More frequently, organization or simple softening of the clot occurs. When organization takes place the mass of fibrine is first permeated from without inward by leucocytes. As these increase and fill the clot the fibrine disappears, and finally is completely replaced by embryonic cells which subsequently are transformed into fibrous tissue. The apparent melting away of the fibrine when invaded by leucocytes, is probably due to their digestion of it and appropriation of it as nourishment.

When such clots undergo simple softening and not organization, we cannot name so confidently the agent by which the softening is accomplished. Living cells do not play an important part in the process. For, according to the usual description, the clot is not filled with such cells, nor does the liquid composing the softened centre contain them. It may be said that, if in this case living cells do not cause liquefaction, there is no reason to suppose that they do in the former. The only answer that can yet be given is, that, from the fact that the fibrin, when organization occurs, disappears just in proportion as it is invaded by leucocytes, and begins to disappear about the edges and along lines where the leucocytes are most numerous, it would seem probable that their presence influences its disappearance.

The removal of fibrinous masses in this way is also seen in the changes that occur in the absorption of the exudate which fills the air cells of the lungs in croupous pneumonia. In the first stage of croupous pneumonia the alveoli contains serum, red and white blood cells, and desquamated pulmonary epithelium. After a time coagulation takes place, fibrin filaments appearing and binding together the cells. This constitutes the stage of red hepatization. As resolution begins the red corpuscles disappear, and hence the lung becomes decolorized and gray. The other cells become fatty. Many of the white corpuscles present the appearances of pus cells. Simultaneously with these latter changes leucocytes migrate freely from the vessels and mingle with the liquefying exudate. The lymph channels are crowded often with granular white corpuscles that undoubtedly have found their way back from the alveoli loaded with its contents. It is thus that resolution takes place under the influence of actively vital leucocytes in patients who scarce expectorate any of the exudate that has filled considerable areas of their lungs.

Cellular digestion in pathological processes is probably illustrated again in the separation of dead from living tissue when sloughs and sequestra are formed. The line of demarcating inflammation is filled with leucocytes, which apparently attack the dead tissue, and undoubtedly the dead cells in the inflamed zone; thus leading to the production of a line of separation or a solution of continuity in the solid structures. Indeed, the most important phenomenon of inflammation is the migration of leucocytes from the vessels and the filling of the tissues by them. In the lowest animals, which do not possess a blood vascular system, the process that is analogous to inflammation in vertebrates consists in the unusual activity and massing of amœboid cells about the source of irritation. The activity of these cells is for the purpose, if possible, of removing or destroying the irritant. The purpose is furthered in higher animals by the first outpouring of serum, since often the irritant is thus dissolved or diluted so as to destroy or neutralize its toxic power. When the serous exudate is inefficacious it becomes the function of the white corpuscle to attempt to remove the irritating body, if solid, either by transporting it granule by

granule to a distance, and thus lessening its amount, or by digesting it and producing chemical changes that will alter its character. Inflammation from this standpoint is a conservative process. While the process is conservative, it is provoked by those things that cause always some destruction of tissue, or of the cells composing it. Even the simplest trauma that may provoke inflammation, and whose action may only be momentary, causes destruction of tissue elements. The removal of these is probably the duty and reason for the migration of the leucocytes. They accomplish the object by transforming the albuminous substance of the dead cells into soluble substances, or by appropriating them to their own nutrition.

The behavior of the leucocytes in the walls of abscesses suggests that in the forming of such cavities they take an important part. The tissue cells are probably destroyed by the cause of the purulent inflammation, but their removal cannot be thus accounted for, and as they disappear only in the presence of leucocytes, and in proportion to the abundance of the latter they would seem dependent on them for solution. Lining the abscess cavity are found a mass of round cells which, by becoming detached and mingled with the fluid contents, are transformed into pus cells. As we pass outward from the cavity these round cells are at first so abundant as to be the only visible elements; further out they are infiltrating tissue that is in an atrophying or disintegrating condition, and in proportion as we pass from the centre the infiltrating cells are less numerous and the normal cells more perfect and natural, until the healthy tissue is reached.

Metchnikoff has urged that the leucocytes are the natural enemy of pathogenic bacteria He points to the numerous examples that have come under the notice of pathologists, of the occurrence of bacteria within the white blood cells. He thinks that this is brought about by an attempt on the part of the leucocyte to destroy and remove the offending body. This endeavor is not always successful, for the protoplasm of the white cells seems to be a favorite place for the growth of some bacteria, but when it is successful recovery takes place. Metchnikoff first described the absorption of bacteria by leucocytes in a fungoid disease which attacked Daphniæ, or water-fleas.* The colorless corpuscles of the Daphnia could be watched as they attacked, devoured and digested the foreign substances. When anthrax bacilli were introduced into the tissues of frogs similar changes were produced, the leucocytes devouring and causing the disappearance of the bacilli.† The examination of two fatal cases of erysipelas‡ showed the cocci free in the tissues, never enclosed in cells. However, in numerous convalescent cases they were found in great numbers enclosed in leucocytes. Thus imbedded, all stages of transition, from fresh, apparently normal cocci to those consisting of mere grain-like detritus, could be observed. That leucocytes remove bacilli that are dead or inactive is quite evident, but that they are generally inimical to bacteria, or that they generally attempt to destroy them, is not proven. For instance, the experiments of Dirckinck-Holmfeld with anthrax bacilli, whose virulence was made of different degrees by Pasteur's method, show that when introduced subcutaneously into rats, cats, etc., it produces local suppuration, and more perfectly in proportion as it has been weakened, or as the animal is resistant to it. He, therefore, in agreement with Metchnikoff, regards the purulent inflammation as a conservative process. But he did not agree with him as regards the mode of destruction of the bacilli. He found only a few of the microörganisms in the pus cells and many in the fluid of the pus, where they died and disintegrated. The bacilli in pus in the animals most resistant to them underwent changes according to the age of the inflammation. In pus twenty-four hours old they were shorter and thicker than natural and surrounded by a clear, capsule-like zone. These rods grew well on culture media and were fatal to mice. In pus forty-eight

---

* Sutton, J. B., "Introductory to General Pathology," p. 123.

† *Virchow's Arch.*, Bd. 97, Seit 502. ‡ *Virchow's Archiv*, CVII, 2, p. 209, 1887.

hours old the bacilli had become finely granular, many even mere granules or short, glistening, often irregularly formed rings. They were no longer capable of cultivation nor toxic to mice. Living bacilli were found very exceptionally in older pus. In reply to the query whether the bacilli had not been first swallowed and destroyed by the pus cells, and subsequently disgorged, the author urged the lesson of the following experiment. If pus containing living bacilli is sealed in a tube that is kept at 36° C. from forty-eight to seventy-two hours the changes above described will take place, but if bacilli growing in bouillon is similarly treated, they lose neither life nor toxicity. He supposed that the pus cells cease to be active, living factors when thus treated. It is evident, however, that the richly cellular pus is inimical to the bacilli, and probably if the cells are not their destroyers, something resulting from the presence of the cells is.

While calling attention to the utility of intra-cellular digestion in pathological processes, I have mentioned only the white blood cells as possessing the power. Undoubtedly connective tissue cells and granulation tissue cells, or embryonic cells, also possess it, and probably some forms of tumor cells.

It is a well-known fact that inflamed or dead bone will undergo absorption unless suppuration intervenes. Numerous theories have been propounded to explain the phenomena. Rindfleisch has suggested that the blood in the congested vessels contains an excess of carbonic acid, which may dissolve the lime salts, forming an acid carbonate.* Others have supposed that lactic acid is formed, which produces a soluble calcic sarcolactate. These hypotheses are improbable, for bone exposed indefinitely to the influences of purulent inflammation loses little of its substance and its surface may remain smooth. Virchow believes that cells derived from proliferation of bone corpuscles are the active agents. There is little doubt that the living cells which surround or permeate bone when it is undergoing absorption are the active factors in its removal, although most pathologists do not wholly agree with Virchow as to their origin. Usually the absorption power is ascribed to granulation cells or to osteoclasts, both of which originate from leucocytes. To illustrate, recall the appearance of the changes that occur in rarefying osteitis. The bone is indented by deep or shallow, simple or complex depressions that are filled with cells of varying size. These cells originate as do granulation cells, but among them giant cells are oftener found than in ordinary granulations. Frequently they are continuous with or outgrowths of neighboring granulation tissue. These so-called osteoclasts fill the pockets in the bone, which so evidently melts before their encroachments that no one can doubt their activity in its removal. It is literally eaten away by them.

Tumor cells are so various in character that we cannot affirm of all kinds digestive power, but some undoubtedly possess this function. The cells of infiltrating tumors have absorptive powers. This capability is most noticeable when bone is involved, for then the hard, compact bone is readily seen to have disappeared and to have been replaced by the new tumor tissue. When tumor cells infiltrate other tissues, the normal cells are seen to undergo atrophy and to finally disappear and be replaced by the tumor structures. This process is ordinarily explained by assigning to the growing tumor a mechanical power of interfering with the blood supply of the neighboring tissue, and therefore inducing atrophy. However, the disappearance of inert lime deposits in bone can scarcely be explained in this way. The influence of the contact of active, growing cells seems more important.

Can living cells render solid materials soluble by simple contact with them? There is little doubt that intra-cellular digestion takes place. But in the absorption of bone there is no evidence that particles of it are first detached, swallowed and then digested by the osteoclasts. On the contrary, the latter apparently erode it by their contact.

---

* Pepper, A. J., "Surgical Pathology," p. 234.

In this respect they behave as do many bacteria, which liquefy solid culture media by the changes incident to their own multiplication and growth while in contact with them. The living cell thus behaves like an organized ferment. When, however, the substance to be removed is granular, the granules are generally taken within the cell before solution or digestion occurs. It would, therefore, be better to describe these processes by the term *cellular digestion*, rather than by the more limited appellation used by Metchnikoff, of intra-cellular digestion.

In the course of such digestion, it is probable that various chemical decompositions are produced and new bodies formed, according to the nature of the substances attacked and the needs of the digesting cell. What these chemical changes are we do not know. There are, however, a few facts that may throw light on the subject or form a starting-point for an investigation to elucidate it. It seems probable that leucocytes have a predilection for peptones, and if so, the thought suggests itself whether this is not the form in which they require their nourishment, and whether its formation is not the first step in the process of cellular digestion by them. Hofmeister believes that in the subepithelial tissue of the digestive tract leucocytes take up peptone that has been formed in the alimentary canal.* That they play an important part in the absorption of nutriment is evident, since they are much more numerous during digestion than at other times, and it is known that they take up the emulsified fat and aid in its transportation. The absence from the blood, during digestion, of dissolved peptone is most easily accounted for, upon the supposition that it has been appropriated by the cellular elements. Hofmeister has also shown that the peptone which is found in pus is contained in the corpuscles.† There is no evidence as yet, however, that peptone can be produced by the corpuscles, since in the wall of the intestines it is furnished to them already formed, and also probably in pus. For the microörganisms peculiar to the latter have the power of forming peptone from albumins on which they are grown. The streptococcus pyogenes, when grown in a vacuum on white of egg or on beef albumin, causes their disintegration and energetic peptonization.‡ The micrococcus pyogenes aureus also converts albumins into peptones.§

The peptone in pus may, therefore, be formed by its bacteria and absorbed by its corpuscles.

If these views in regard to cellular digestion are true, we must recognize among bodies foreign to the living tissues a group of digestible substances. We can then classify foreign bodies into : 1, soluble bodies; 2, insoluble but digestible bodies; 3, insoluble, granular and transportable bodies; 4, insoluble bodies, completely impregnable to leucocytes and the surrounding tissues.

DISCUSSION.

Dr. DANFORTH thanked Dr. Davis for his very able and scholarly paper, but thought its scope was too narrow—that the digestive power alluded to was not limited to the leucocytes alone, but that the nuclei of all the tissues took part in the process. In traumatic states all the tissues become embryonic—the nuclei are liberated by the softening of their surrounding primal material, and become "amœboid" cells, or practically leucocytes. These amœboid cells acquire the digestive power which Dr. Davis claims for leucocytes alone.

---

* "Zeitschrift für Phys. Chemie," 4, pp. 253–281; 5, pp. 127–151; 6, pp. 51–73.

† "Studies from the Biological Laboratory, Johns Hopkins University," Vol. IV, No. 1, pp. 8–10. ‡ "Crookshank's Practical Bacteriology." § *Ibid.*

Dr. SHAKESPEARE regretted that he had not heard the paper just communicated, but he inferred from the discussion that the cellular organisms active in the process of destruction and repair of the tissues were under consideration. He wished to call attention to some observations he had the opportunity to announce in a series of lectures before the College of Physicians of Philadelphia, an abstract of which was published some years ago in the *Medical News*, of Philadelphia. The subject of those lectures was the intimate nature of inflammation in the non-vascular tissues. The minute normal structure of the cornea and hyaline cartilages was revised as a foundation for the study of inflammation of them. He had found, with Thin, of London, that the ultimate bundles of fibrils in the cornea, as recognized by most histologists, have not the simple constitution commonly described. There is a further subdivision of the fibrils into much smaller bundles. But the point he wished to call especial attention to is the fact that each of these minute smaller bundles is enveloped more or less completely by a single layer of exceeding small, thin, flat cells, resembling, in shape and relations to each other and to the bundles which they cover, the flat, fixed cells which we are very well acquainted with in silver and gold-treated pieces of tendon. The apposition of three or more of these minute bundles causes the formation of linear lymph spaces, parallel with the direction of the bundles.

I found, with Thin, and Spina, of Austria, that hyaline cartilage is not the simple structure so commonly described, but that it has a framework of fibrous connective tissue which is normally masked by the hyaline substance which envelops, and by similarity of index of refraction renders the real complex structure ordinarily invisible. I have found the same minute bundles of fibrils and their enveloping, minute, thin, flat, fixed cells, as in the cornea. I may say that they are to be found also in bone and in the central nervous system.

Now, what I wish to say is, that in the non-vascular tissues I have found these minute, flat, fixed cells in the immediate vicinity of the point of irritation, showing all the evidences of reawakened activity, viz., cloudy swelling and division, accompanied by the signs of softening, to a slight extent, it is true, of the fibrils with which they are in contact, in advance of the invasion of the emigrant white blood cells. In advanced inflammation the progeny of these cells, with that of the recognized common fixed cells and the emigrant cells of the blood, constitute the mass of cells in the so-called embryonal tissue which replaces the normal structure, and it becomes impossible to definitely settle the origin of any single one of them. Dr. Shakespeare holds that these minute, thin, flat cells, which may be regarded as fixed, play an exceedingly important rôle, either in destruction or repair, possibly in both.

Dr. N. S. DAVIS, Jr., closing the discussion, said:—Dr. Danforth has remarked that I limited the power of cellular digestion too closely. I wish to state that my feeling is that other tissue elements contribute to the so-called absorption process, but on thinking over the various pathological lesions, I could find no illustration of digestion by the higher forms of cells, but only by those of embryonic form. The suggestion of Dr. Danforth and of Dr. Shakespeare, that the higher forms of tissue elements, under conditions of inflammation, return to an embryonic state not distinguishable from wandering blood cells, and then exert the same function, may be true.

To the question of Dr. Vaughn, whether any chemical ferment had been isolated in the cells, I can only say that in my search through the literature of the subject I have found no evidence of the existence of such substances.